ORIGINAL RESEARCH

Wilms tumour among children attending Mbarara Regional Referral Hospital: Clinico-pathological characteristics and outcome at the end of treatment

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East Cent Afr J Surg. 2019 Apr;24(1):28–34
https://dx.doi.org/10.4314/ecajs.v24i1.5

Abstract

Background
Wilms tumour (WT) is the commonest malignant renal tumour in children and most common solid tumour in Africa. In Sub-Saharan Africa it is the commonest intra-abdominal tumour. WT is the commonest abdominal solid tumour in children in Mbarara Regional Referral Hospital (MRRH). Survival is determined by tumour histology, tumour biology, stage at diagnosis and surgery. In our settings other factors that may determine treatment outcome include; availability of chemotherapy and radiotherapy, co-morbidity, blood transfusion and anaesthesia. There is however no information regarding the clinico-pathological characteristics and treatment outcome of WT in MRRH. This study therefore set out to determine clinico-pathological characteristics of WT and end of treatment outcome among children attending this hospital.

Methods
A retrospective medical record review of all children diagnosed with WT at MRRH between January 2014 and March 2016 was done. Ten patients who had been diagnosed with WT between April 2016 and December 2016 and also receiving treatment at MRRH were recruited prospectively into the study. Data on various sociodemographics, clinical findings, histological characteristics and treatment outcome were collected. For data collected retrospectively patients were called in for follow up.

Results
Records of 14 patients were reviewed retrospectively, and 10 patients were recruited (prospectively). Of these two, were lost to follow up. Male to female ratio was 1:1. Mean age at diagnosis was 46 months. All the patients presented with an abdominal mass. Sixty seven percent presented in the pathological stage I and II of WT. Sixty seven percent of the patients had unfavourable histology, and of these, 63% had diffuse anaplasia. Only 59% were alive at the end of treatment.

Conclusions
Our patients are similar with regard to gender ratio, mean age at diagnosis, age distribution as described in literature. However, our patients differ in histological characteristics with a big proportion having anaplasia compared to WT studies done elsewhere. Majority of the patients were alive at the end of treatment.

Keywords: Wilms tumour, clinico-pathological characteristics, outcomes

Introduction

Wilms tumour (WT), which is also known as nephroblastoma, is the commonest malignant renal tumour in children (Atteby Y et al, 2014). In Africa, WT is the commonest solid tumour (Stefan D. C, 2015) and in Sub-Saharan Africa it is the commonest intra-abdominal tumour in children (Emmanuel A et al, 2011).

There are about 7.6 cases of WT per million children below age 15 years world-wide (Emmanuel A et al, 2011). In the United States of America, where the vast majority of children are cured, it affects more than 400 children annually (Humberto L, 2001). In South Africa, the incidence of WT is 5.4 per million children below 15 years, with about 2.9-6.2 per million per province (Aronson D.C. et al, 2014). In Uganda, WT represents approximately 6.8 percent of cancers

that present to the Uganda Cancer Institute, UCI (Stefan D. C, 2015), making it the most common childhood solid tumour treated at UCI. It is also the commonest childhood solid tumour treated at MRRH (MRRH Oncology unit, 2015).

More than 80% of WT are diagnosed in children below five years of age (Szychot E. et al, 2014). It is rare in children less than 6 months of age or above 10 years of age (Ehrlich P. F., 2007) and has a peak incidence at 3 years of age (Aronson D.C. et al, 2014).

Event-free and overall survival for children diagnosed with WT depends on the stage of disease at diagnosis and histology. There are two major divisions of WT histology, favorable histology and unfavorable. Favorable histology comprises of epithelial, blastemal and stromal while unfavorable histology includes anaplasia, which can be diffuse or focal. Anaplasia is found to occur in about 10% of patients and the presence of anaplasia is a poor prognostic marker (Faranoush M.et al, 2009).

Most people with WT can be cured with multi-modal therapy (chemotherapy, radiation and surgery) and there after live a normal life (Faranoush M. et al, 2009).

Cure rates in developed countries exceed 90% for non-metastatic disease, and remain above 80% even for stage 4 and 5 (Ehrlich P. F., 2007). Improvements in the cure rate of WT have been the result of a number of factors that include improvements in surgical technique, recognition of the sensitivity of WT to radiation and chemotherapy agents, and applying results from previous multidisciplinary clinical research trials (Ehrlich P. F., 2007).

In low-income and middle income countries (LMICs), the cure rates are less than 20% (Rodriguez-Galindo C. et al, 2013). Studies done in low income countries found the end of treatment outcome ranging from 11% to 61% (Paintsil et al, 2015). This is attributed to delayed presentation, failure to access or complete the treatment, incomplete investigations and probably unfavourable histological characteristics.

It is important to note that some progress has been made in the treatment of children with WT in Africa through local capacity building and addressing the social and financial barriers to care (Israels T. et al, 2012).

Successful management of WT requires proper staging of the tumour and collaboration among different specialties such as paediatric cancer specialists, surgeons, radiologists, pathologists, and radiation specialists (Szychot E. et al, 2014). Surgery is the cornerstone of WT management (Uba A. F. et al, 2007). Surgery plays a critical role in the management of WT; so it is of great importance that the procedure is performed by experienced Surgeons, and are patients managed at specialized centres (Szychot E. et al, 2014).

There are many groups that run clinical trials for WT; NWTSG (National Wilms Tumor Study Group), which has since been replaced by COG (Children's Oncology Group), SIOP (International Society of Pediatric Oncology) and a few other national study groups. There are a few key differences regarding the timing of surgery and chemotherapy in these protocols (Dome J. S. et al, 2015). In the COG, which runs in North America, the traditional approach to a renal mass in a child is nephrectomy followed by chemotherapy and possibly radiotherapy (Morgenstern B. Z et al, 2004). SIOP, which runs in most of Europe, recommends neoadjuvant chemotherapy, followed by tumour resection; with additional treatment given as necessary. The primary difference in the two studies is the timing of the surgical resection. However, both approaches produce similar survival rates (Dome J. S. et al, 2015). Other treatment modalities include chemotherapy for all stages and radiotherapy for stage 3 and 4 (Breslow. N. E. et al, 2006).

The most commonly used drugs in the management of WT are Vincristine, Actinomycin and Doxorubicin (Warwick A. B et al, 2010). Following the NWTSG protocol, post-operative chemotherapy is based on the individual tumour's histology and stage at surgery. Actinomycin and Vincristine are used in the treatment of localized disease; for metastatic disease Doxorubucin is added to the regimen (Israels T. et al, 2012). High risk patients also receive radiotherapy to the tumour bed (Szychot E. et al, 2014).

However, WT treatment protocols function best when adopted to local circumstances (Szychot E. et al, 2014). In Mulago National Referral hospital (MNRH), the WT management is done according to the SIOP protocol. The treatment protocol at MRRH is modeled on individual patients, that is, treatment is determined on a patient by patient basis with some children undergoing upfront Nephrectomy followed by chemotherapy, started at least four weeks after surgery and then given over a period of six months while others get neoadjuvant chemotherapy prior to performing nephrectomy (MRRH oncology unit, 2015).

MRRH and Mbarara University of Science and Technology (MUST) recently opened an oncology unit and a paediatric surgery unit that together jointly manage WT patients.

This study was conducted to evaluate outcomes from WT treated at a rural hospital in Uganda and access the impact of histologic features on survival.

Methods

Study design

This was an observational study. It had a retrospective component and a prospective component. This was in order to be able to attain the sample size within the given research period. The research was a retrospective review of records of children diagnosed with WT over the past 2 years and a prospective study of patients diagnosed with WT over the following one year.

For the retrospective part of the study, families of patients previously diagnosed with WT were contacted and the patients followed up while for the prospective part, the research team was involved in the clinical diagnosis, surgery and follow up of all patients diagnosed with WT. For the retrospective part patients were called by phone and a standardized questionnaire filled for the information that was not available in the chart review.

Table 1. Demographic characteristics

Characteristic		n (%)
Gender	Male	12(50%)
	Female	12(50%)
Address	Bushenyi	5(21%)
	Mbarara	3(12%)
	Kasese	3(13%)
	Others	13(54%)
Age category	<2 years	7(29%)
	>2 years	17(71%)
Referral status	IN	15(62%)
	OUT	3(13%)

Study Area

The study was conducted at Mbarara Regional Referral and Teaching Hospital in the Paediatric surgery and the Oncology units. The hospital is a 425 bed capacity serving as a regional referral hospital with Surgical, Medical, Obstetrics and Gynaecology, Paediatric, ENT, Dental, Orthopedic and other specialized units for example, the oncology unit.

Study subjects

Children with a histopathological diagnosis of WT at MRRH over a three year period looking at two years retrospectively and one year prospectively.

Sample size

A total of 24 patients were included in the study.

Ethical considerations

Study was approved by IRB and permission was granted from MRRH administration to conduct these studies.

Results

Demographics

Overall a total of 24 patients were recruited into this study, whereby 10 recruited prospectively and 14 patients' records were reviewed retrospectively and included in this study. Two patients (8%) were lost to follow up. The mean age of the cohort was 46 months with a range of 14 to 96 months.

All the children presented with an abdominal mass, and nephrectomy was the most common procedure performed. For those that had hematuria, no tumour cells were found in the ureters. None underwent cystoscopy. Majority of the patients had early pathological stage of WT, stage I 5(21%) and stage II 11(46%). Four patients with stage III had positive lymph nodes for malignancy while 1 patient with stage IV had a positive lymph node. The histology was mostly unfavorable. The weights of kidney-tumour were quite high with a mean of 787.75 grams, mode of 500 grams and a range from 354 grams to 2400 grams. Surgical procedures were completed for many of the patients within one week of being admitted to the paediatric surgery unit.

Of the 24 children, 13(54%) completed chemotherapy. There was no syndromic child in this study.

Histological characteristics

Of the 24 patients, 8 (33%) had favorable histology and 16(67%) had unfavorable histology.

The patients had their histology subtypes detailed and 43% of these were found to be blastemal.

A weight of kidney-tumour specimen of more than 550 grams was significantly determined to have anaplasia among this cohort (Pvalue 0.013).

Of the 16 patients with unfavorable histology, most had diffuse anaplasia 10(63%) while the rest were focal.

Outcomes at the end of treatment

Of the 22 patients followed up, 13(59%) were alive while 9 (41%) had died by the end of treatment.

The median follow up time was 6 months. No child died from the complications of surgery. Of those alive at the end of treatment, 4 were stage I, 8 stage II and 1 was stage III. Among the patients that had unfavorable histology, 7(43.8%) died. Ninety two percent of those that completed chemotherapy were alive. Of those that died, 7(87.5%) had not completed chemotherapy.

Five patients that had neoadjuvant chemotherapy had passed away by the end of treatment.

Of the 9 patients that died, 7 had anaplasia while two had favorable histology.

Discussion

A total of 24 patients were involved in this study. Twenty three had unilateral tumors, and one girl had bilateral tumors. None of the patients was syndromic. Sixty seven percent had anaplasia, and 63% of those with anaplasia had diffuse anaplasia. Of the 22 patients followed up, 59% were alive at the end of the end of treatment.

Clinical characteristics

Age

Among these patients, the mean age at diagnosis was 46 (CI 35.73-56.76) months, with the youngest child having 14 and the oldest had 96 months. The mode was 60 months.

Eighty percent of the children presented before 5 years of age.

This current study is comparable to others performed worldwide. In a study completed in Morocco, mean age of patients with WT was 36 months (Madani A. et al, 2006) and Abuidris D. O. et al, 2008 found that the mean age to be 4.1 years. Stones D. K. et al, 2015, Dumoucel. S. et al, 2014, Emmanuel. A. et al, 2011 and Warwick. A. B et al in 2010 all had similar findings.

Table 2. Clinical characteristics

Variable	Characteristic	n(%)
Presentation	Abdominal mass	24(100%)
	Abdominal pain	10(42%)
	Weight loss	10(42%)
	Hematuria	5(21%)
	Fever	9(37%)
Nature of surgery	Nephrectomy	22(92%)
	Trucut biopsy	2(8%)
Pathological stage	I	5(21%)
	II	11(46%)
	III	5(21%)
	IV	2(8%)
	V	1(4%)
Histological characteristics	Favorable	8(33%)
	Unfavorable	16(67%)
Weight of kidney-tumour specimen	<550 grams	8(50%)
	>550 grams	8(50%)
Period between admission and surgery	<1 week	16(67%)
	>1 week	8(33%)
Completed chemotherapy	Yes	13(54%)
	No	10(41%)

This is also in line with other studies that show 75% of WT presented before 5 years of age (Aronson. D. C et al, 2014) and steadily declines with increasing age (Stephanie S. et al, 2006).

Gender

In this study, there were an equal number of males and females.

Similar findings have been found in studies performed in other parts of the world such as Madani. A. et al, 2006, Stones. D. K. et al, 2015, Abuidris. D. O et al, 2008, Warwick. A. B et al, 2010 and Emmanuel. A. et al in 2011.

Presentation

All the patients in the study presented with an abdominal mass. The second most common manifestation was weight loss and abdominal pain each at 40%, this was followed by fever (36%) and the least was hematuria (20%).

This is in conformity with several studies like that carried out by Abuidris. D. O, et al, 2008 that found abdominal mass being the most common presentation in WT. Other studies with similar findings are Uba A. F et al, 2007 in Nigeria, Fadoo. Z et al, 2009 at Aga Khan University Hospital in Pakistan and Ehrlich. P. F., 2007.

Abdominal mass was the most common presenting symptom because it is the easiest noticeable symptom by the caregivers. Hematuria would also be a very late sign signifying the tumour has invaded the major calyces and the ureters or bladder, and yet most tumours arise from either pole.

Stage of disease

The study found that 67% (I, 21%; II, 46%) of the patients had early pathological stage WT while 33% (III, 21%; IV, 8%; V, 4%) presented with late stage, demonstrating that majority of the patients who came to MRRH had early pathological stage of WT.

This is comparable with findings by Maher K. M. M et al, 2014 in Jordan, where they found that there were 62.3% of the WT cases presenting in stage I and II. Also in a Malawi study by Israels. T et al, 2012, the stages of disease at pathology were, 12 (24%) with stage I, 20 (39%) had stage II, while 19 (37%) had stage III. Abd el-aal. H. H et al, 2005 in Egypt, found that majority of the WT patients presented in stage I and II.

On the contrary, many studies performed in Africa have shown that late presentation is common for example in Nigeria, 72% were stages III and IV (Hadley. L.G. P et al, 2012), and in Sudan 78% were stages III and IV (Abuidris. D. O et al, 2008). So did Kanyamuhunga. A et al, 2015 in Rwanda and Njuguna. F et al in 2016 in Kenya

The difference in stage at presentation was because here, it was the pathological stage and not the disease stage of the patient as reported by the pathologist on analysis of the biopsy specimens. The biopsy taken for all patients who had Nephrectomy included paracaval or paraaortic lymph node sampling and the ureter.

Also, some patients here presented early because of the free medical services offered by the hospital.

Weight of kidney-tumour specimen

The average weight of specimen was 787.5 grams with a mode of 500 grams and a range from 354 grams to 2400 grams. The weight being more or less than 550 grams had no association with the outcome.

Israels T et al, 2012, in a Malawi study found that tumour weight was ranging from 30 g to 3000g, with a mean tumour weight of 750g. Atanda. A. T et al, 2015, in Nigeria reported similar findings.

International Society of Pediatric Oncology 6 and 9 WT trials and studies found that the average kidney-tumour weight was 612 grams with a range from 65 grams to 3500 grams as found by Vujanic. G. M. et al, 1999.

The tumour being bulky suggests fast growth rate and with this increased chance of the tumour rupturing before the surgical operation or during the operation. Also, the weight of kidney tumour being high could be attributed to the different genetics seen in WT among patients seen in Sub-Saharan Africa in comparison to patients elsewhere.

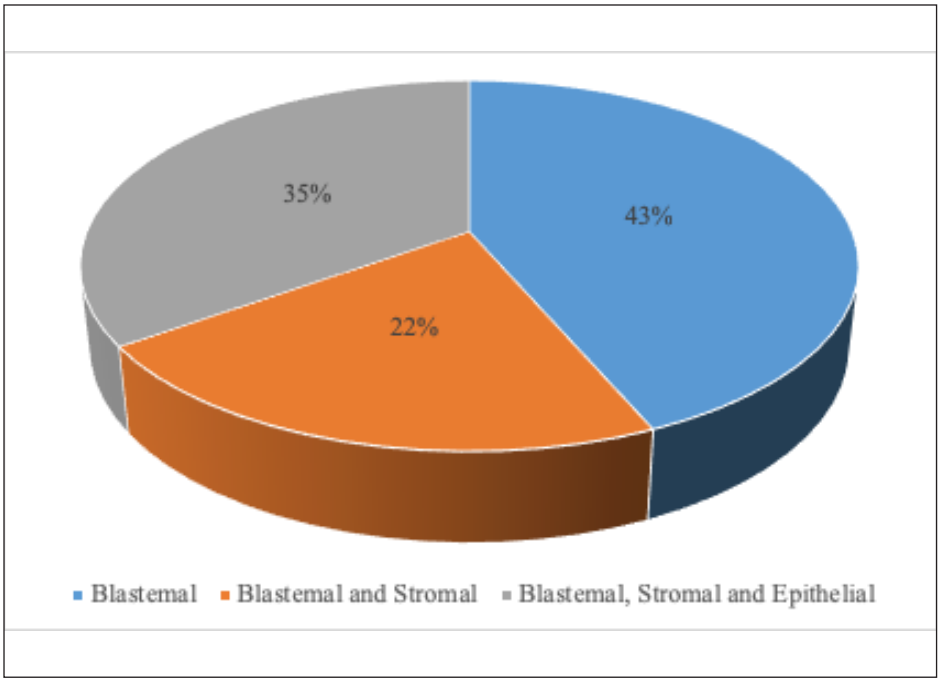

Figure 1. Histological subtypes among the patients

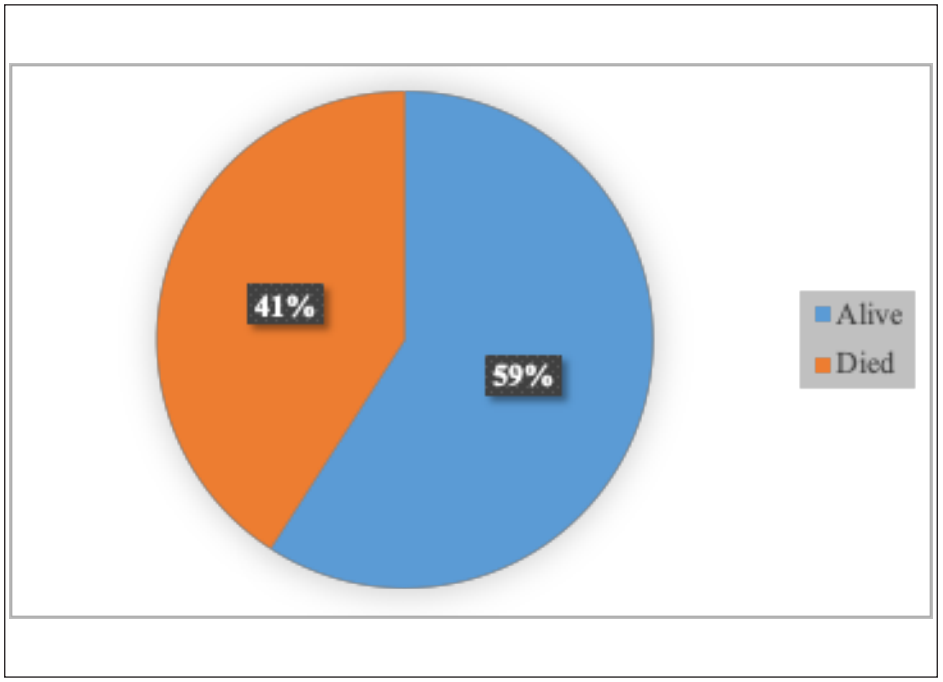

Figure 2. Patient outcomes at the end of Wilms tumour treatment

Histological characteristics

Most of the patients, 67% had unfavorable histology. Of these, 63% had diffuse anaplasia. When the histological subtypes were analysed, majority were blastemal –monophasic (43%), followed by Epithelial, Stromal and Blastemal (triphasic) type which constituted 35% and then Blastemal and Stromal (22%). There was none that was stromal predominant.

This is different from other studies carried out elsewhere, as other studies have found more patients with favorable histology than unfavorable histology.

Seyed-Ahadi. M-M et al, 2007 found favorable histology in 54.5% and unfavorable histology in 43.6% in WT patients during a study performed at Mofid Children's Hospital in Tehran. Other studies with more favorable histology are Abd el-aal. H. H, et al, 2005 in Egypt, Rabeh W. et al, 2016 in Lebanon and Maher K. M. M et al, 2014 in Jordan.

On histological subtypes, a study done in Kenya, by Murphy. A. J et al in 2012, found that blastemal predominant WT was 53.3%. While an Egyptian study by Salama A. et al, in 2011 found that the most common subtype at 49.2% was blastemal morphology.

However, Vujanic. G. M et al, 1999 found that 54.7% were mixed type, 29.1% Blastemal, 3.5% Epithelial and 2.3% were stromal predominant type while Vujanic. G. M et al, 2003, noted that 23% were mixed, 15% blastemal, 6% epithelial and 16% stromal, 17% completely necrotic and 23% had marked chemotherapy induced changes.

However, Weirich. A. et al, 2001 reported Epithelial predominant 15.5%, Stromal predominant 0%, Blastemal predominant 39.4% and Mixed (Triphasic) 45.1%.

All this shows the contrast in histological findings when compared to findings in MRRH.

A study done in Kenya, by Murphy. A. J et al, 2012 reported that in Sub-Saharan Africa, WT may have unique biological phenotype that is associated with more mortality and having more treatment resistance in comparison with other places in the world and hence findings in the MRRH study could also be explained by the different genetics seen among the WT in patients in Sub-Saharan Africa. This explains the high anaplasia rate in our institutional findings.

Blastemal monophasic type was seen because WT is an embryonal tumour caused by abnormal renal development stemming from proliferation of metanephric blastema.

Outcomes

By the end of WT treatment, only 59% of the patients were alive. Comparing with other studies around the world, this is a relatively fair outcome following the treatment for WT and similar or higher to some in LMICs.

All the patients that had neoadjuvant therapy died. This can be attributed to their late presentation to the hospital whereby they had metastasis.

Several studies have shown post treatment survival for WT to range from 11% to 43% such as Abuidris. D.O et al, 2008 in Sudan, Uba. A. F et al, 2007 in Nigeria, Abd el-aal. H. H et al, 2005, in Egypt with some even having survival above 80%, for example Rabeh W. et al, 2016 in Lebanon and Maher K. M. M et al, 2014 in Jordan.

These studies are in contrast to our institutional observations. Hence showing that more children survive here after getting treated for WT compared to some places in Africa, however, lower survival rates compared to the developed world.

The low survival rates are attributable to the high occurrence of anaplasia among our patients. Also diffuse anaplasia is more common here than the focal anaplasia. All of which are poor prognostic factors.

Also, blastemal type has been associated with aggressive disease while presence of anaplasia has been associated with chemotherapy resistance. The low survival rates here can also be attributed to the lack of radiotherapy services in Uganda at the time when these children were receiving treatment, which is required in management of advanced stage WT.

Conclusion

In conclusion, the number of children presenting to MRRH with WT is comparable to other centres around the world. Most of the children diagnosed at MRRH have unfavorable histology as compared to European and American centers that treat WT patients.

The children that are treated at MRRH for WT had a poorer outcome, with only 59% alive at the end of treatment as compared to the developed world.

Those patients that completed chemotherapy had better outcomes as did those that had early stage at diagnosis.

Acknowledgements

We acknowledge the members of the Department of Surgery at Mbarara University of Science and Technology, staff of the Oncology unit, staff of the Paediatric surgery ward, our research assistants and MRRH.

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Peer Reviewed (Uncorrected Proof)

Competing Interests: None declared.

Received: 2 Jan 2018 • **Revised:** 10 Jun 2018

Accepted: 11 Dec 2018 • **Published**: 30 Apr 2019

Cite this article as: Okello I, Tibenderana R, Lubega A, Tuhairwe E, Situma M. Wilms tumour among children attending Mbarara Regional Referral Hospital: Clinico-pathological characteristics and outcome at the end of treatment. E Cent Afr J Surg. 2019;24(1):28-34. https://dx.doi.org/10.4314/ecajs.v24i1.5.